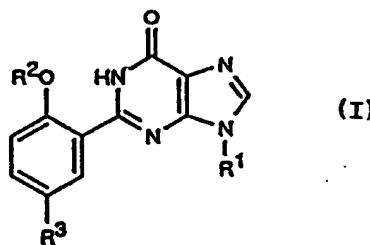




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(54) Title: PURINONE ANTIANGINAL AGENTS



(57) Abstract

Compounds of formula (I), and pharmaceutically acceptable salts thereof, wherein R¹ is C₁-C₄ alkyl; R² is C₂-C₄ alkyl; R³ is H or SO₂NR⁴R⁵; R⁴ and R⁵ together with the nitrogen atom to which they are attached form a pyrrolidino, piperidino, morpholino or 4-N-(R⁶)-1-piperazinyl group; and R⁶ is H or C₁-C₃ alkyl; are selective cGMP PDE inhibitors useful in the treatment of, *inter alia*, cardiovascular disorders such as angina, hypertension, heart failure and atherosclerosis.

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PURINONE ANTIANGINAL AGENTS

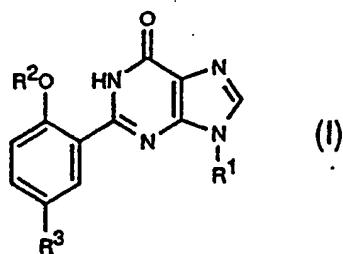
This invention relates to a series of purin-6-ones, which are potent and selective inhibitors of cyclic guanosine 3',5'-monophosphate phosphodiesterase (cGMP PDE), having utility in a variety of therapeutic areas including the treatment of cardiovascular disorders such as angina, hypertension, heart failure and atherosclerosis.

The compounds of the invention exhibit selectivity for inhibition of cGMP PDEs rather than cyclic adenosine 3',5'-monophosphate phosphodiesterases (cAMP PDEs) and, as a consequence of this selective PDE inhibition, cGMP levels are elevated, which in turn can give rise to beneficial anti-platelet, anti-neutrophil, anti-vasospastic and vasodilatory activity, as well as potentiation of the effects of endothelium-derived relaxing factor (EDRF) and nitrovasodilators. Thus the compounds have utility in the treatment of a number of disorders, including stable, unstable and variant (Prinzmetal) angina, hypertension, pulmonary hypertension, congestive heart failure, atherosclerosis, conditions of reduced blood vessel patency e.g. post-percutaneous transluminal coronary angioplasty (post-PTCA), peripheral vascular disease, stroke, bronchitis, allergic asthma, chronic asthma, allergic rhinitis, glaucoma, and diseases characterised by disorders of gut motility, e.g. irritable bowel syndrome (IBS).

Australian patent application AU-A-10956/88 and European patent application EP-A-0352960 disclose certain purin-6-ones which, unlike the compounds of the present invention, are N-unsubstituted in the imidazole portion of the purinone bicyclic system. These prior art purinones are reported to be selective cGMP PDE inhibitors with bronchodilator and vasodilator

activity, of value in combatting asthma, bronchitis, angina, hypertension and congestive heart failure. However, compared with the 9-alkylpurin-6-ones of the present invention, they are not particularly potent cGMP PDE inhibitors.

The compounds of the present invention have the formula (I):



and pharmaceutically acceptable salts thereof,
 wherein R^1 is $\text{C}_1\text{-C}_4$ alkyl;
 R^2 is $\text{C}_2\text{-C}_4$ alkyl;
 R^3 is H or $\text{SO}_2\text{NR}^4\text{R}^5$;
 R^4 and R^5 together with the nitrogen atom to which they are attached form a pyrrolidino, piperidino, morpholino or 4-N-(R^6)-1-piperazinyl group;
 and R^6 is H or $\text{C}_1\text{-C}_3$ alkyl.

In the above definition, unless otherwise indicated, alkyl groups having three or more carbon atoms may be straight chain or branched chain.

The compounds of formula (I) may contain one or more asymmetric centres and thus they can exist as stereoisomers, i.e. as enantiomers or as diastereoisomers. The invention includes both mixtures thereof and the separated individual stereoisomers.

The compounds of formula (I) may also exist in

tautomeric forms and the invention includes both mixtures thereof and the separated individual tautomers.

Also included in the invention are radiolabelled derivatives of compounds of formula (I) which are suitable for biological studies.

The pharmaceutically acceptable salts of the compounds of formula (I) are, for example, non-toxic acid addition salts formed with inorganic acids such as hydrochloric, hydrobromic, sulphuric and phosphoric acid, with organo-carboxylic acids, or with organo-sulphonic acids. Compounds of formula (I) can also provide pharmaceutically acceptable metal salts, in particular non-toxic alkali metal salts, with bases. Examples include the sodium and potassium salts. For a review on suitable pharmaceutical salts, see *J. Pharm., Sci.*, 1977, 66, 1.

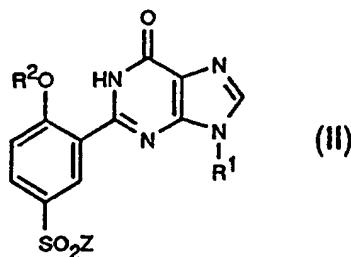
A preferred group of compounds of formula (I) is that wherein R¹ and R² are each independently ethyl or n-propyl; R⁴ and R⁵ together with the nitrogen atom to which they are attached form a 4-N-(R⁶)-1-piperazinyl group; and R³ and R⁶ are as previously defined.

A particularly preferred group of compounds of formula (I) is that wherein R¹ is n-propyl; R² is ethyl; and R³ is 1-piperazinylsulphonyl or 4-methyl-1-piperazinylsulphonyl.

In another aspect, the present invention provides processes for the preparation of compounds of formula (I) and pharmaceutically acceptable salts thereof, as hereinafter described.

(A) A compound of formula (I), wherein R³ is SO₂NR⁴R⁵, may be obtained from a compound of formula (I) wherein R³ is H, and R² and R³ are as previously defined for formula (I). This can be achieved via the intermediacy

of a sulphonyl halide of formula (II):



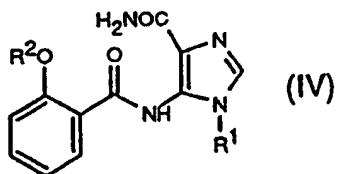
wherein Z is halo, preferably chloro, and R¹ and R² are as previously defined for formula (I), by reaction with an amine of formula (III):



wherein R⁴ and R⁵ are as previously defined for formula (I). The reaction is generally carried out at ambient temperature, preferably in the presence of a solvent, e.g. a C₁-C₃ alkanol, using about a 5-fold excess of (III) to scavenge the acid by-product (HZ) and, in the case of piperazine (R⁶ is H), to minimise bis-sulphonamide formation.

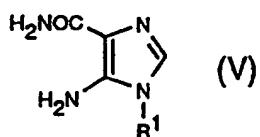
A compound of formula (II) is obtainable by the application of known methods for the introduction of a SO₂Z group into a benzene ring; for example, when Z is chloro, by the action of excess chlorosulphonic acid at from about 0°C to about ambient temperature.

A compound of formula (I) wherein R³ is H, R¹ and R² are as previously defined for formula (I), may be obtained from a compound of formula (IV):

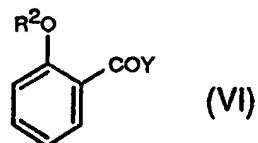


wherein R¹ and R² are as previously defined for formula (I), by the application of known cyclisation methods for pyrimidinone ring formation. Thus, for example, cyclisation may be effected by the treatment of (IV) with a base such as sodium hydroxide or potassium carbonate, optionally in the presence of excess hydrogen peroxide, in an ethanol-water medium, at about the reflux temperature of the reaction medium. Alternatively, cyclisation may be effected with polyphosphoric acid at about 140°C.

A compound of formula (IV) may be prepared from a compound of formula (V):

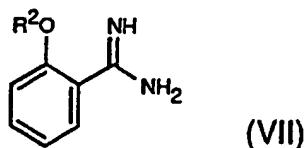


wherein R¹ is as previously defined for formula (IV), by reaction with an acyl halide of formula (VI):



wherein Y is halo, preferably chloro or bromo, and R² is as previously defined for formula (IV). The reaction is generally carried out using from about 1 to about 2 equivalents of (VI) in the presence of an excess of a tertiary amine such as triethylamine or pyridine to act as scavenger for the acid by-product (HY), optionally in the presence of a catalyst such as 4-dimethylaminopyridine, in an inert solvent such as dichloromethane, at from about 0°C to ambient temperature for 2-72 hours. For convenience, pyridine may also be used as solvent.

Alternative methods of converting (V) to a compound of formula (I) wherein R³ is H, and R² and R³ are as previously defined for formula (I), will be evident to persons skilled in the art. For example, a one-step procedure involves the reaction of (V) with an amidine of formula (VII):

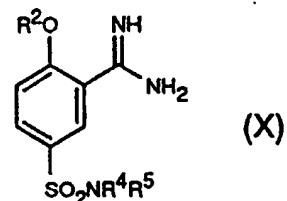
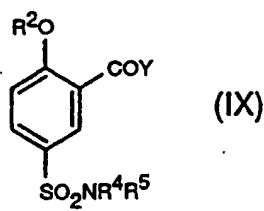


wherein R² is as previously defined for formula (I), at elevated temperature. The aminoimidazolecarboxamide

component may be in the form of an acid addition salt, e.g. the hydrochloride, and the reaction may be conducted in the absence of solvent, or in a suitable solvent such as a C₁-C₄ alcohol, pyridine or N-methyl-pyrrolidone, at from about 65°C to about 200°C.

A compound of formula (V) may be prepared from an amine of formula R¹NH₂ (VIII), wherein R¹ is as previously defined for formula (V), and 2-amino-2-cyanoacetamide in a two-stage process, according to the procedure disclosed in EP-A-66,909. Firstly, the latter component is condensed with a tri-lower alkyl orthoformate, e.g. trimethyl or triethylorthoformate, in a suitable solvent such as acetonitrile, at the reflux temperature of the reaction medium, then the intermediate formimidate is treated in situ with (VIII) at about ambient temperature. 2-Amino-2-cyanoacetamide can be obtained by dithionite reduction of ethyl 2-cyano-2-(hydroxyimino)acetate, followed by in situ amination of the intermediate ethyl 2-amino-2-cyanoacetate, as reported in Chem. and Ind., 1980, (13), 541.

(B) A compound of formula (I), wherein R³ is SO₂NR⁴R⁵, may be obtained more directly from a compound of formula (V) by employing an acyl halide of formula (IX) or an amidine of formula (X):



wherein R², R⁴ and R⁵ are as previously defined for formula (I) and Y is as previously defined for formula

(VI), in reactions analogous to those described above for (VI) and (VII) respectively.

(C) A compound of formula (I) may also be obtained from the corresponding phenol precursor, i.e. a compound of formula (I) wherein R² is H and R¹ and R³ are as previously defined for formula (I), thereby introducing R² at the final stage of the synthesis. This may be achieved by selective O-alkylation of the phenolic group under standard conditions, using the appropriate C₂-C₄ alkyl bromide, iodide or sulphonate, in the presence of a base such as anhydrous potassium carbonate, in a suitable solvent, e.g. 2-butanone, at from about ambient temperature to about the reflux temperature of the reaction medium. Alternatively, the alkylation may be effected under typical Mitsunobu reaction conditions. A variety of other selective O-alkylation procedures will be obvious to persons skilled in the art.

(D) Certain piperazines of formula (I), wherein R⁶ is as previously defined for formula (I) but is not hydrogen, may be prepared directly from the corresponding 4-N-unsubstituted piperazine analogue, i.e. the precursor wherein R⁶ is H, by standard alkylation procedures such as use of the appropriate C₁-C₃ alkyl bromide, iodide or sulphonate, in the presence of a base such as anhydrous potassium carbonate, in a suitable solvent, e.g. 2-butanone, at from about ambient temperature to about the reflux temperature of the reaction medium.

Compounds of formulae (VI), (VII), (IX) and (X), and the various reagents required for the processes hereinbefore disclosed, when neither commercially available nor subsequently described, can be obtained by conventional synthetic procedures, in accordance

with standard textbooks on organic chemistry or literature precedent, from readily accessible starting materials using appropriate reagents and reaction conditions.

Moreover, persons skilled in the art will be aware of variations of, and alternatives to, those processes described hereinafter in the Examples and Preparations sections such that all the compounds defined by formula (I) are obtainable.

The pharmaceutically acceptable acid addition salts of the compounds of formula (I) which contain a basic centre may also be prepared in a conventional manner. For example a solution of the free base is treated with the appropriate acid, either neat or in a suitable solvent, and the resulting salt isolated either by filtration or by evaporation under vacuum of the reaction solvent. Pharmaceutically acceptable base addition salts can be obtained in an analogous manner by treating a solution of a compound of formula (I) with the appropriate base. Both types of salt may be formed or interconverted using ion-exchange resin techniques.

The biological activities of the compounds of the present invention were determined by the following test methods.

Phosphodiesterase activity

Compound affinities for cGMP and cAMP PDEs are assessed by determination of their IC_{50} values (the concentration of inhibitor required for 50% inhibition of enzyme activity). The PDE enzymes are isolated from rabbit platelets and rat kidney, essentially by the method of W.J. Thompson *et al.* (Biochem., 1971, 10, 311). The calcium/calmodulin (Ca/CAM)-independent cGMP PDE and the cGMP-inhibited cAMP PDE enzymes are

obtained from rabbit platelets whilst, of the four major PDE enzymes of the rat kidney, the Ca/CAM-dependent cGMP PDE (fraction I) is isolated. Assays are performed using a modification of the "batch" method of W.J. Thompson and M.M. Appleman (Biochem., 1979, 18, 5228). Results from these tests show that the compounds of the present invention are potent and selective inhibitors of both cGMP PDEs.

Platelet anti-aggregatory activity

This is assessed by the determination of a compound's ability to inhibit platelet aggregation in vitro induced by platelet activating factor (PAF), and to potentiate the platelet antiaggregatory action in vitro of activators of guanylate cyclase such as nitroprusside and EDRF. Washed platelets are prepared essentially by the method of J.F. Mustard et al. (Methods in Enzymol., 1989, 169, 3) and aggregation is determined using standard turbidimetric techniques as described by G.V.R. Born, (J. Physiol. (Lond), 1962, 162, 67P).

Antihypertensive activity

This is assessed following intravenous or oral administration of a compound to spontaneously hypertensive rats. Blood pressure is recorded via a cannula implanted in the carotid artery of either conscious or anaesthetised animals.

For administration to man in the curative or prophylactic treatment of angina, hypertension or congestive heart failure, oral dosages of the compounds will generally be in the range of from 4-800 mg daily for an average adult patient (70 kg). Thus for a typical adult patient, individual tablets or capsules contain from 2-400 mg of active compound, in a suitable pharmaceutically acceptable vehicle or carrier, for administration in single or multiple doses, once or several times per day. Dosages for intravenous, buccal

or sublingual administration will typically be within the range of from 1-400 mg per single dose as required. In practice the physician will determine the actual dosing regimen which will be most suitable for an individual patient and it will vary with the age, weight and response of the particular patient. The above dosages are exemplary of the average case but there can be individual instances in which higher or lower dosage ranges may be merited, and such are within the scope of this invention.

For human use, the compounds of formula (I) can be administered alone, but will generally be administered in admixture with a pharmaceutical carrier selected with regard to the intended route of administration and standard pharmaceutical practice. For example, they may be administered orally, buccally or sublingually, in the form of tablets containing excipients such as starch or lactose, or in capsules or ovules either alone or in admixture with excipients, or in the form of elixirs or suspensions containing flavouring or colouring agents. The compounds may also be injected parenterally, for example intravenously, intramuscularly, subcutaneously or intracoronarily. For parenteral administration, they are best used in the form of a sterile aqueous solution which may contain other substances, for example salts, or monosaccharides such as mannitol or glucose, to make the solution isotonic with blood.

Thus the invention provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable diluent or carrier.

The invention also provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition containing either entity, for use in medicine.

The invention further provides the use of a

compound of formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition containing either entity, for the manufacture of a medicament for the treatment of stable, unstable and variant (Prinzmetal) angina, hypertension, pulmonary hypertension, congestive heart failure, atherosclerosis, stroke, peripheral vascular disease, conditions of reduced blood vessel patency, chronic asthma, bronchitis, allergic asthma, allergic rhinitis, glaucoma or diseases characterised by disorders of gut motility.

In a further aspect, the invention provides a method of treating or preventing stable, unstable and variant (Prinzmetal) angina, hypertension, pulmonary hypertension, congestive heart failure, atherosclerosis, stroke, peripheral vascular disease, conditions of reduced blood vessel patency, chronic asthma, bronchitis, allergic asthma, allergic rhinitis, glaucoma or diseases characterised by disorders of gut motility, in a mammal (including a human being), which comprises administering to said mammal a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition containing either entity.

The invention also includes any novel intermediates of formulae (II) and (IV) disclosed herein.

The syntheses of the compounds of the invention and of the intermediates for use therein are illustrated by the following Examples and Preparations. The purity of the compounds was routinely monitored by thin layer chromatography (TLC) using Merck Kieselgel 60 F₂₅₄ plates. ¹H-Nuclear magnetic resonance (NMR) spectra were recorded using either a Nicolet QE-300 or a Bruker AC-300 spectrometer and were in all cases

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consistent with the proposed structures.

Ambient temperature means 20-25°C.

EXAMPLE 12-(2-Ethoxyphenyl)-9-n-propylpurin-6-one

A solution of 5-(2-ethoxybenzamido)-1-n-propylimidazole-4-carboxamide (Preparation 3; 0.35 g, 0.0011 mol) in ethanol (8 ml) was added to a stirred mixture of aqueous hydrogen peroxide (30% solution; 0.3 ml, 0.0026 mol), water (15 ml) and sodium hydroxide (0.2 g, 0.005 mol). The resulting mixture was heated at 90°C for 7 hours, stirred at ambient temperature for a further 15 hours, then evaporated under vacuum. The residue was dissolved in water (20 ml), and the resulting solution acidified with hydrochloric acid to pH 4 and then extracted with dichloromethane (2 x 30 ml). The combined organic extracts were washed with water (25 ml), dried (MgSO_4) and evaporated under vacuum to give the title compound, which crystallised from ethyl acetate as a colourless solid (0.17 g, 52%), m.p. 172-174°C. Found: C, 64.57; H, 6.15; N, 18.99. $\text{C}_{16}\text{H}_{18}\text{N}_4\text{O}_2$ requires C, 64.41; H, 6.08; N, 18.78%.

EXAMPLE 22-[2-Ethoxy-5-(1-piperazinylsulphonyl)phenyl]-9-n-propylpurin-6-one

2-(2-Ethoxyphenyl)-9-n-propylpurin-6-one (0.5 g, 0.00167 mol) was added portionwise to ice-cold chlorosulphonic acid (3 ml) and the mixture stirred at ambient temperature for 15 hours. The resulting solution was added cautiously to stirred ice/water (50 g) and the mixture extracted with dichloromethane (2 x 50 ml). The combined organic extracts were dried (MgSO_4), then evaporated under vacuum to give 2-(5-chlorosulphonyl-2-ethoxyphenyl)-9-n-propylpurin-6-one (0.63 g) which was used without further purification.

A mixture of piperazine (0.36 g, 0.0041 mol), the preceding sulphonyl chloride (0.31 g, 0.00078 mol) and ethanol (15 ml) was stirred at ambient temperature for 15 hours, then evaporated under vacuum. The residue

was chromatographed twice on silica gel (12 g) using a dichloromethane:methanol:aqueous ammonia elution gradient (95:5:0 to 90:10:0 to 90:10:1) to give the title compound, which crystallised from acetonitrile as a colourless hydrated solid (0.19 g, 55%), m.p. 174-176°C. Found: C, 53.22; H, 6.08; N, 18.56. $C_{20}H_{26}N_6O_4S$; 0.25 H₂O requires C, 53.26; H, 5.92; N, 18.63%.

EXAMPLE 3

2-[2-Ethoxy-5-(4-methyl-1-piperazinylsulphonyl)phenyl]-9-n-propylpurin-6-one

The title compound was prepared from 2-(2-ethoxyphenyl)-9-n-propylpurin-6-one and 1-methyl-piperazine, following the procedure of Example 2, and was obtained as a colourless solid (81%), m.p. - softens at 150°C. Found: C, 54.94; H, 6.30; N, 17.92. $C_{21}H_{28}N_6O_4S$ requires C, 54.76; H, 6.13; N, 18.25%.

PREPARATION 12-Amino-2-cyanoacetamide

Ethyl 2-cyano-2-(hydroximino)acetate (30.0 g, 0.21 mol) was dissolved in a stirred mixture of saturated aqueous sodium bicarbonate solution (90 ml) and water (180 ml), and sodium dithionite (102 g, 0.59 mol) was then added portion-wise. The resulting mixture was stirred at ambient temperature for 0.5 hour, then extracted with dichloromethane (4 x 200 ml). The organic extracts were combined, washed with saturated brine (200 ml), dried (Na_2SO_4) and evaporated under vacuum. The residue was stirred at ambient temperature for 1 hour with aqueous ammonia solution (SG 0.880, 250 ml) and, after cooling, the resulting solid was collected by filtration and dried under vacuum to give the title compound as a colourless solid (2.8 g, 13%), m.p. 123-125°C. Rf 0.12 (SiO₂; dichloromethane: methanol:aqueous ammonia, 90:10:1).

PREPARATION 25-Amino-1-n-propylimidazole-4-carboxamide

A mixture of 2-amino-2-cyanoacetamide (2.8 g, 0.0282 mol), trimethylorthoformate (3.4 g, 0.0321 mol) and acetonitrile (55 ml) was heated under reflux for 0.75 hour, then allowed to cool. n-Propylamine (1.8 g, 0.0305 mol) was then added dropwise, and the resulting mixture stirred at ambient temperature for 36 hours. The solid which precipitated was collected by filtration and crystallised from methanol to give the title compound as a colourless solid (2.9 g, 61%), m.p. 241-243°C. Found: C, 49.67; H, 7.15; N, 33.64. $\text{C}_7\text{H}_{12}\text{N}_4\text{O}$ requires C, 49.98; H, 7.19; N, 33.31%.

PREPARATION 35-(2-Ethoxybenzamido)-1-n-propylimidazole-4-carboxamide

Oxalyl chloride (1.74 g, 0.137 mol) was added dropwise to a stirred solution of 2-ethoxybenzoic acid

(1.1 g, 0.00663 mol) and dimethylformamide (0.1 ml) in dichloromethane (20 ml) and the resulting mixture stirred at ambient temperature for 4 hours, then evaporated under vacuum. The residue was azeotroped with dichloromethane (2 x 20 ml), then added dropwise to a stirred solution of 5-amino-1-n-propylimidazole-4-carboxamide (0.9 g, 0.00536 mol) in pyridine (20 ml). The resulting solution was stirred at ambient temperature for 3 days, then evaporated under vacuum. The residue was dissolved in dichloromethane (50 ml), and the solution washed with 1N hydrochloric acid (30 ml), dried (Na_2SO_4) and evaporated under vacuum. Chromatography of the crude product on silica gel (15 g) using a methanol in dichloromethane elution gradient (2-6% methanol), followed by crystallisation from ethanol, gave the title compound as a colourless solid (1.3 g, 77%), m.p. 182-184°C. Found: C, 60.85; H, 6.40; N, 18.06. $\text{C}_{16}\text{H}_{20}\text{N}_4\text{O}_3$ requires C, 60.74; H, 6.37; N, 17.71%.

Biological activity

The following Table illustrates the in vitro activities for the compounds of the invention.

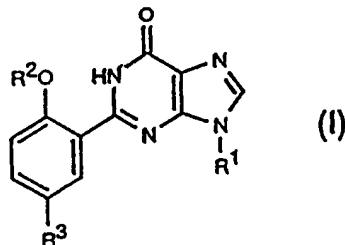
TABLEIN VITRO PDE INHIBITORY DATA:

SELECTIVITY BETWEEN CALCIUM/CALMODULIN (Ca/CAM)-INDEPENDENT cGMP PDE AND cGMP-INHIBITED cAMP PDE

EXAMPLE	IC ₅₀ (nM)		SELECTIVITY RATIO
	cGMP	cAMP	
1	97	>100,000	>1,030
2	16	100,000	6,250
3	6.4	80,000	12,500

CLAIMS

1. A compound of formula (I):



or a pharmaceutically acceptable salt thereof,

wherein R¹ is C₁-C₄ alkyl;

R² is C₂-C₄ alkyl;

R³ is H or SO₂NR⁴R⁵;

R⁴ and R⁵ together with the nitrogen atom to which they are attached form a pyrrolidino, piperidino, morpholino or 4-N-(R⁶)-1-piperazinyl group;

and R⁶ is H or C₁-C₃ alkyl.

2. A compound according to claim 1 wherein R¹ and R² are each independently ethyl or n-propyl; and R⁴ and R⁵ together with the nitrogen atom to which they are attached form a 4-N-(R⁶)-1-piperazinyl group.

3. A compound according to claim 2 wherein R¹ is n-propyl; R² is ethyl; and R³ is 1-piperazinylsulphonyl or 4-methyl-1-piperazinylsulphonyl.

4. A pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof, according to any one of claims 1 to 3, together with a pharmaceutically acceptable diluent or carrier.

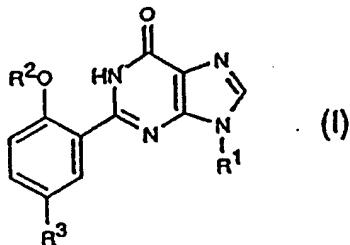
5. A compound of formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition containing either entity, according to any one of claims 1 to 4, for use in medicine.

6. The use of a compound of formula (I), or a

pharmaceutically acceptable salt thereof, or a pharmaceutical composition containing either entity, according to any one of claims 1 to 4, for the manufacture of a medicament for the treatment of stable, unstable and variant (Prinzmetal) angina, hypertension, pulmonary hypertension, congestive heart failure, atherosclerosis, stroke, peripheral vascular disease, conditions of reduced blood vessel patency, chronic asthma, bronchitis, allergic asthma, allergic rhinitis, glaucoma or diseases characterised by disorders of gut motility.

7. A method of treating or preventing stable, unstable and variant (Prinzmetal) angina, hypertension, pulmonary hypertension, congestive heart failure, atherosclerosis, stroke, peripheral vascular disease, conditions of reduced blood vessel patency, chronic asthma, bronchitis, allergic asthma, allergic rhinitis, glaucoma or diseases characterised by disorders of gut motility, in a mammal (including a human being), which comprises administering to said mammal a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition containing either entity, according to any one of claims 1 to 4.

8. A process for the preparation of a compound of formula (I):



or a pharmaceutically acceptable salt thereof,

wherein R¹ is C₁-C₄ alkyl;

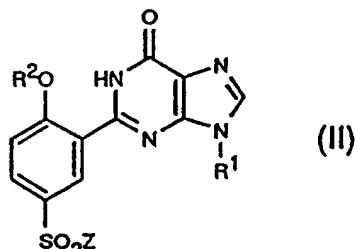
R² is C₂-C₄ alkyl;

R³ is SO₂NR⁴R⁵;

R⁴ and R⁵ together with the nitrogen atom to which they are attached form a pyrrolidino, piperidino, morpholino or 4-N-(R⁶)-1-piperazinyl group;

and R⁶ is H or C₁-C₃ alkyl;

which comprises reacting a compound of formula (II):



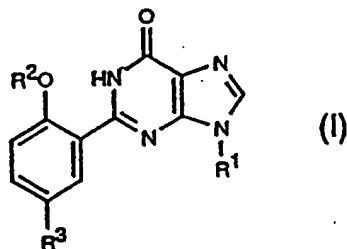
wherein Z is halo, and R¹ and R² are as previously in this claim, with a compound of formula (III):



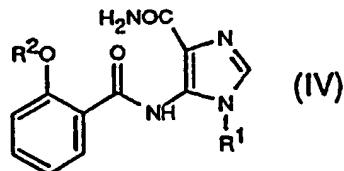
wherein R⁴ and R⁵ are as previously defined in this claim, and optionally converting the required product to a pharmaceutically acceptable salt thereof.

9. A process according to claim 8 wherein a 5-fold excess of a compound of formula (III) is employed together with a C₁-C₃ alkanol as solvent.

10. A process for the preparation of a compound of formula (I):



or a pharmaceutically acceptable salt thereof,
 wherein R¹ is C₁-C₄ alkyl;
 R² is C₂-C₄ alkyl;
 and R³ is H;
 which comprises cyclisation of a compound of formula (IV):



wherein R¹ and R² are as previously defined in this claim.

11. A process according to claim 10 wherein the cyclisation is achieved using a base, optionally in the

presence of excess hydrogen peroxide, in aqueous ethanol.

12. A process according to claim 11 wherein the base is sodium hydroxide or potassium carbonate.

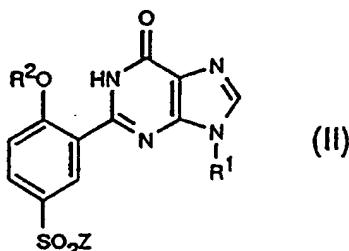
13. A process according to claim 8 or claim 9 wherein R¹ and R² are each independently ethyl or n-propyl; and R⁴ and R⁵ together with the nitrogen atom to which they are attached form a 4-N-(R⁶)-1-piperazinyl group.

14. A process according to claim 13 wherein R¹ is n-propyl; R² is ethyl; and R³ is 1-piperazinylsulphonyl or 4-methyl-1-piperazinylsulphonyl.

15. A process according to any one of claims 10 to 12 wherein R¹ and R² are each independently ethyl or n-propyl.

16. A process according to claim 15 wherein R¹ is n-propyl and R² is ethyl.

17. A compound of formula (II):



wherein Z is halo, and R¹ and R² are as previously defined in claim 8.

18. A compound according to claim 17 wherein Z is chloro.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 93/01561

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ⁶		
According to International Patent Classification (IPC) or to both National Classification and IPC Int.Cl. 5 C07D473/30; A61K31/52		
II. FIELDS SEARCHED		
Minimum Documentation Searched ⁷		
Classification System	Classification Symbols	
Int.Cl. 5	C07D	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁸		
III. DOCUMENTS CONSIDERED TO BE RELEVANT ⁹		
Category ¹⁰	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
A	US,A,5 073 559 (WILLIAM J. COATES) 17 December 1991 *Document* ---	1-18
A	GB,A,1 338 235 (MAY & BAKER) 21 November 1973 *Document* ---	1-18
A	EP,A,0 347 146 (SMITH KLINE & FRENCH LABORATORIES) 20 December 1989 *Document* ---	1-18
A	EP,A,0 352 960 (SMITH KLINE & FRENCH LABORATORIES) 31 January 1990 cited in the application *Document* ---	1-18
		-/-
<p>¹⁰ Special categories of cited documents : ¹¹ "A" document defining the general state of the art which is not considered to be of particular relevance ¹² "B" earlier document but published on or after the international filing date ¹³ "C" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) ¹⁴ "D" document referring to an oral disclosure, use, exhibition or other means ¹⁵ "E" document published prior to the international filing date but later than the priority date claimed ¹⁶ "F" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention ¹⁷ "G" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step ¹⁸ "H" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art ¹⁹ "I" document member of the same patent family </p>		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search 21 SEPTEMBER 1993	Date of Mailing of this International Search Report 27.09.93	
International Searching Authority EUROPEAN PATENT OFFICE	Signature of Authorized Officer LUYTEN H.W.	

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
Category	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
A	EP,A,0 293 063 (SMITH KLINE & FRENCH LABORATORIES) 30 November 1988 *Document* & AU,A,8 810 956 (SMITH KLINE & FRENCH LABORATORIES) cited in the application -----	1-18
A		

INTERNATIONAL SEARCH REPORT

International application No.

PCT/EP 93/01561

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
Although claim 7 is directed to a method of treatment of (diagnostic method practised on) the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. Claims Nos.: because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO.

EP 9301561
SA 75744

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information. 21/09/93

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
US-A-5073559	17-12-91	None		

GB-A-1338235	21-11-73	AT-B- 319235 AT-B- 317211 AT-A, B 315839 AT-A, B 315838 AU-B- 458277 AU-A- 3686771 BE-A- 841181 BE-A- 776683 CA-A- 1026755 CH-A- 552610 CH-A- 555351 CH-A- 550814 CH-A- 556860 CH-A- 546779 DE-A, C 2162096 DE-A- 2618694 FR-A, B 2118078 GB-A- 1493685 LU-A- 64457 NL-A- 7604548 NL-A- 7117142 OA-A- 3930 SE-B- 393381 US-A- 3987160 US-A- 4039544 US-A- 3819631	10-12-74 26-08-74 15-05-74 15-05-74 20-02-75 21-06-73 27-10-76 14-06-72 21-02-78 15-08-74 31-10-74 28-06-74 13-12-74 15-03-74 06-07-72 11-11-76 28-07-72 30-11-77 23-08-72 01-11-76 19-06-72 14-08-75 09-05-77 19-10-76 02-08-77 25-06-74	

EP-A-0347146	20-12-89	AU-B- 612852 AU-A- 3635789 JP-A- 2042079 US-A- 5047404	18-07-91 21-12-89 13-02-90 10-09-91	

EP-A-0352960	31-01-90	AU-B- 613503 AU-A- 3821089 JP-A- 2088577	01-08-91 25-01-90 28-03-90	

EP-A-0293063	30-11-88	AU-B- 599452 AU-A- 1095688	19-07-90 04-08-88	

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ON INTERNATIONAL PATENT APPLICATION NO.

EP 9301561
SA 75744

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0293063		DE-A- 3869205	23-04-92
		JP-A- 63196585	15-08-88
		US-A- 4885301	05-12-89
		ZA-A- 8800680	03-08-88